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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/600,521	08/27/2001	Jianyun Dong	22488-710	7109

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EXAMINER	
AKHAVAN, RAMIN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 09/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No. 09/600,521	Applicant(s) DONG ET AL.	
	Examiner Ramin (Ray) Akhavan	Art Unit 1636	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 25 August 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 6 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *47,58,59,61,67-69,71-73 and 115-119*.

   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☒ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

4,07

ADVISORY ACTION

Receipt is acknowledged of a response, filed 08/25/2005, amending claim 61 and traversing the rejections of record. Claims 47, 58, 59, 61, 67-69, 71-73 and 115-119 are pending in this application. The amendment to claim 61 is entered.

Applicant's arguments have been fully considered but are not deemed persuasive. The rejections of record are set forth under 35 U.S.C. §112, first paragraph. More particularly, the rejections consist of a rejection of claims 118 and 119 under 35 U.S.C. §112 (Deposit Requirement) and a rejection of all the claims as lacking enablement for *in vivo* use.

35 USC §112 - Deposit Requirement

With respect to the Deposit Requirement, Applicant asserts that the instant specification teaches the sequences for the structural elements that are to be mobilized into intermediate vectors whose sequence maps are readily available. Thus, Applicant asserts one of skill will be able to construct the specific vectors of claims 118 and 119. (e.g., Remarks, p. 8, ¶¶ 1-2). In sum, Applicant asserts that since the maps of the intermediate vectors are available and the specification teaches the sequence of FasL placed downstream of the GFP sequence, then claims 118 and 119 are enabled.

It is respectfully pointed out that each claim is directed to a specific vector, which is necessarily defined by a specific sequence of nuclei acids. That the maps of intermediate vectors are available is of little moment, because even a single nucleotide change (e.g., utilizing different restriction sites within the cloning site of an intermediate vector) would distinguish vectors that otherwise have the requisite structural elements (e.g., tet-responsive element, GFP, FasL).

Put another way, by claiming a specific vector, each claim is defined by a specific sequence for said vector. Therefore, a single unique sequence would correspond to the claimed vector in each of claims 118 and 119. As such, one of skill in the art cannot construct a specific vector without knowledge of the specific sequence for said vector (e.g., variance in cloning sites). The rejection is maintained.

35 USC §112 - Enablement In Vivo

With respect to rejections based on a lack of enablement for practicing the invention *in vivo*, Applicant's assertions are summarized as follows: (1) the apoptotic effect induced via FasL expression will be localized to the tumor and not affect normal cells (Remarks, p. 10, paragraph 1, last sentence); (2) some of the cited art does not support the grounds of rejection (Remarks, p. 10, paragraph 2, first sentence; p. 11, second full paragraph); (3) systemic administration of adenoviral vectors comprising tissue specific and inducible promoters will limit expression of FasL to a particular locus, i.e. tumor cells (Remarks, p. 12, paragraph 1), and is demonstrated to be nonlethal; and (4) direct injection of the adenovirus vector into solid tumors in mice demonstrates therapeutic potential and no lethal effects (Remarks, p. 13, second full paragraph).

At the outset, it should be noted that as written, the claims read on systemic administration of adenoviral vectors to induce cell death in Fas^+ cells. In other words, the claims are not exclusively delimited to direction injection of the vectors into a tumor mass. For example, independent claim 47 is broadly directed to "transducing an adenoviral vector ...into cancer cells".

Thus, the vector can be administered through any route. Similarly, claim 61 is directed to "direction injection of the adenoviral vector among cancer cells". Thus, injection by any route into a patient within whom cancer cells are present meets this claimed limitation.

Applicants first assertion is that the specification teaches a method of treating a tumor by introducing a vector expressing FasL into a second tumor cell, whereby the expressed FasL then interacts with a second tumor cell that is Fas^+ thus inducing apoptosis in said second tumor cell (i.e., bystander effect). None of the claims are so delimited. However, irrespective of what cancer cells are transduced, the unpredictability is borne from systemic administration *and* immunotoxicity of utilizing adenoviral vectors in gene therapy. (e.g., Final Action, mailed 05/17/2005, p. 7, ¶¶ 2-3). Therefore, at least within the context of systemic delivery adenoviral vectors, the immunotoxicity is exclusive from the therapeutic being expressed.

As noted in the Final Action, there is unpredictability with respect to practicing the invention *in vivo* with respect to vector neutralization via anti-adenoviral antibodies, and immunogenicity affecting transgene expression levels and viral vector distribution within the subject. (Final Action, p. 7, citing Green et al. Canc. Gene Therapy, 2002; 9: 1036-42). For example, the duration of transgene expression can be reduced by the host's anti-virus immune response. Thus, Applicant's assertion that a tissue-specific and an inducible promoter[1] will limit expression to specific target cells is of little moment, where the relevant art suggest that it is unpredictable whether the vector will be delivered to the target in the first place. (Supra, Green, 2002).

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[1] It should noted that the broadest claims are not directed to a tissue specific promoter, where independent claim 47 recites the conjunctive "or" before the limitation "an inducible promoter".

Applicant also presents a reference demonstrating that systemic delivery in immunocompetent mice (BALB/c mice) demonstrates that the vector is safe, does not address the unpredictability with respect to vector-neutralization/biodistribution, which would preclude delivery and expression of the transgene in target cells. First, the evidence is comprised in a post-filing publication. (Applicant's effective priority date is 11/06/1998). Second, results in mice are not necessarily extendable to other mammals (e.g., humans, where the virus may rapidly localize in the liver).

In addition, Applicant provides a Declaration by Dr. James S. Norris, which demonstrates that nude mice are injected with cancer cells resulting in tumors forming in the animals' flanks with subsequent injection into different sites of the tumor of the adenoviral vectors expressing FasL. The FasL expression results in significant regression of the growing tumors. The accuracy or significance of the result is not disputed. However, the Declaration does not provide any additional evidence that is not already present in the instant disclosure.

Applicant's second argument is that the cited references Arai et al. or O'Connell et al. do not suggest unpredictability. It is noted that there are references that do support unpredictability, which have not been addressed in Applicant's arguments. (e.g., supra, Green, 2002; Rossi et al. J. Hematology, 2003; 88: 212-18). With respect to Arai et al., Applicant's argument is persuasive insofar as the inflammation observed at the site of direct injection into tumor mass does not result in toxic effects.

In addition, with respect to O'Connell et al., Applicant asserts that in the mouse model studied, no immune cell death or induction of an inflammatory response is observed as a result of FasL interacting with normal cells that are Fas^{+}.

Further, Applicant asserts that utilizing tissue specific promoters limits expression to target cells only. Applicant's arguments are not found persuasive, because adenovirus can localize to non-target tissue owing to the characteristics of the vector and the host (e.g., localization in liver). Further, the claims are not limited to tissue specific promoters (e.g., independent claim 47), but encompass any inducible promoter. Thus any amount of expression (e.g., leaky expression) will result in FasL expression (e.g., vectors localized in non-target tissue).

With respect to the unintended effects of immune cell death and induction of an inflammatory response (immunotoxicity), Applicant is correct in stating that the specification does not teach that expression of FasL leads to unintended effects of immune cell death or induction of an inflammatory response (e.g., FasL interaction with non-target or normal Fas^+ cells). However, Applicant's examples are limited to expression of FasL in nude mice (immunocompromised). In addition, results in mice would not necessarily translate to predictability for practicing the invention in larger mammals (e.g., human subjects). In any event, O'Connell teaches that there is a reasonable level of unpredictability in expressing a FasL *in vivo* insofar as any Fas^+ cell will interact with the ligand, whereby adverse effects include immune cell death or immunotoxicity.

Applicant's third argument is that systemic administration of a vector with a tissue specific and inducible promoter is demonstrated to be therapeutic and nonlethal. This argument has been addressed in the discussion above of Applicant's first argument. In sum, based on the host (e.g., human) there is unpredictability with systemic administration, as to whether the vector is actually delivered to the desired target cells/tissue.

Thus, regulation of expression would not be determinative with respect to the level of unpredictability. Further, it should be noted, that the claims are not exclusively directed to the adenovector comprising a tissue-specific and inducible promoter (e.g., claim 47).

Applicant's last argument has also been addressed in view of the interpretations of the claims stated above. Applicant asserts that direction injection into the tumor mass demonstrates therapeutic potential and non-lethality. However, as written, the claims are not directed exclusively to direct injection into the tumor mass. Furthermore, results in mice are not necessarily predictive of results that would be observed in immunocompetent and/or larger mammals.

In sum, the amendment to claim 61 is entered. However, neither the amendment nor Applicant's arguments are deemed sufficient to obviate the grounds of rejection of record and discussed in the foregoing. The rejections are maintained.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ramin (Ray) Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached on Monday- Friday from 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully submitted,

Ray Akhavan/AU 1636

DAVID GUZO
PRIMARY EXAMINER